Management Lines of Ankylosing Spondylitis: Updated Overview

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Abstract :

Background: Ankylosing spondylitis (AS) is the chief subtype and a leading outcome of an inter-related cluster of rheumatic disorders named spondyloarthritides (SpAs). Clinical features of this cluster encompass inflammatory back pain, asymmetrical peripheral oligoarthritis (primarily of the lower limbs), enthesitis, and specific organ involvement like anterior uveitis. Aortic root involvement and conduction abnormalities are uncommon complications of ankylosing spondylitis. This disease may lead to structural and functional disorders. In contrast to the synovial membrane inflammation associated with many other arthropathies, such as rheumatoid arthritis (RA), the typical pathology of AS is enthesitis. The entheses are anatomical locations that tolerate heavy mechanical loads, such as fibrocartilaginous joints, the osseous insertions of ligaments and tendons, and joint capsules. The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) guidelines 2019 updates advise that the objectives of axSpA/AS management are: to relieve symptoms, enhance functioning, sustain workability, reduce disease complications, and diminish skeletal damage. NSAIDs and proper rehabilitation programs remain the mainstays of the management of axSpA. The 2016 update of the Assessment of Spondylarthritis International Society (ASAS) and European League Against Rheumatism (EULAR) guidelines advise that patients with pain and stiffness should utilize an NSAID as a first-line treatment up to the full dose while considering hazards and benefits. For patients who improve on NSAIDs, continued use of this medication is favored if on-demand use worsens symptom.

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Introduction:

Ankylosing spondylitis (AS) is the chief subtype and a leading outcome of an inter-related cluster of rheumatic disorders named spondyloarthritides (SpAs). Clinical features of this cluster encompass inflammatory back pain, asymmetrical peripheral oligoarthritis (primarily of the lower limbs), enthesitis, and specific organ involvement like anterior uveitis. Aortic root involvement and conduction abnormalities are uncommon complications of ankylosing spondylitis. This disease may lead to structural and functional disorders. AS is a complex disease linked to several risk factors, both genetic and environmental. Its tendency to repeat within families, first documented in some detail in 1961 **(1).**

- **Delay in Diagnosis**

Females have a significantly longer diagnosis delay than males. Several causes have been described to explain the longer diagnostic delay among females, such as the known discrepancies in the presenting clinical manifestations reported by female patients, such as a lower frequency of characteristic IBP as one of the presenting manifestations, more pronounced upper thoracic and neck or widespread pain, along with the less intense or slower progression of radiographic damage **(2).**

Patients with widespread pain, which occurs in at least 25% of female axSpA patients, are sometimes misdiagnosed as fibromyalgia, as it has some overlapping symptoms with axSpA **(2).**

Comorbidity

According to publications, osteoporosis in AS is estimated to be about two times more elevated than in the general population **(3).**

Osteoporosis more often affects patients with more prominent syndesmophyte formation and a more prolonged disease course; males are more affected than females. In patients with early axSpA, the male sex was a significant predictor of low BMD at the lumbar spine and hip, which has been associated with the radiographic progression of axSpA **(4).**

Osteoporosis in males with AS is frequently underdiagnosed. Several probable explanations can be attributed to this. First, the standard procedure for assessing BMD in the general population is dual-energy X-ray absorptiometry (DXA). However, syndesmophytes at the lumbar spine may falsely elevate BMD measures in individuals with AS. Second, as the majority of patients are diagnosed with AS between the ages of 20 and 40, they are often well below the advised age for screening for low BMD based on current guidelines despite their substantially elevated risk; thus, young males are less likely to be screened according to the practice guidelines. Third, osteoporosis is not usually suspected in a young male patient due to the correlation between raised disease activity and high markers of bone resorption **(5).**

Treatment Response and Drug Adherence

Several analyses demonstrate that AS females have doubled risk of failure of TNF inhibitor (TNFi) compared with males. This variety in the drug's effectiveness among women and men may be

generated by discrepancies in the balance of sex hormones and gene-specific expression likely triggered by X-chromosome instability and gene-specific epigenetic modifications. Further, drug survival of TNFi treatment in patients with AS is inferior in women than in men. Also, women with AS had a shorter treatment duration than men and were more likely than men to change treatment (4).

Some predictors were associated with an adequate therapy response, such as the existence of the HLA-B27, lack of enthesitis, short illness course, and TNFi naive. These predictors were negatively associated with the female gender because females with AS have a more increased prevalence of enthesitis and a more prolonged diagnosis delay. These aspects may cause gender discrepancies in TNFi adherence and response (2).

Musculoskeletal Imaging

Over the last decades, considerable improvement within the area of imaging in axSpA provided different techniques for diagnosing, classifying, and assessing disease activity, structural damage, and prognosis of patients with axSpA. Imaging in AS has been synonymous for decades with CR. However, developments in CT, US, and particularly MRI have dramatically increased the amount and scope of information obtainable by imaging (6).

Conventional Radiography

The conventional radiograph is relatively cheap, available worldwide, and produces an almost identical image regardless of technical parameters or whether the image is analog or digital (6).

To diagnose sacroiliitis associated with axSpA CR of the SIJs is recommended as the first imaging technique. Also, CR of the spine is usually the first imaging modality requested for assessing a patient with LBP of any cause in clinical practice. Initial lumbar and cervical spine CR is recommended in patients with AS to detect syndesmophyte formation. CR of the SIJs and spine may be utilized for long-term structural damage monitoring in axSpA, particularly new bone formation (7).

For radiographic imaging cases with chronic LBP and doubted axSpA, an anteroposterior view of the pelvis region or a Ferguson view is generally taken to estimate sacroiliitis. Oblique views may deliver additional helpful details but need higher radiation levels. Typical radiographic findings result from osteodestructive or osteoproliferative changes caused by chronic inflammation. In the SIJs, they include erosions, pseudo-widening, sclerosis, bony bridging, and/or SIJ ankylosis, and in the spine, vertebral corner erosions, enthesophytes, vertebral squaring, sclerosis and erosions of the vertebral endplate, disk calcifications, spondylophytes, syndesmophytes, bony bridging, and/or intervertebral ankylosis (8).

The SIJs involvements are typically graded from 0 (normal) to 4 (total ankylosis) to determine the nature and severity of the disorder, and such grading is utilized to determine the degree of confidence that the changes seen reflect sacroiliitis. The findings that illustrate each grade are:

●Grade 0: Normal

●Grade 1: Suspicious (but not definite) changes

●Grade 2: Minimal abnormality – Small localized areas with erosions or sclerosis, without alteration in the joint width

●Grade 3: Unequivocal abnormality – Moderate or advanced sacroiliitis with one or more of the following: erosions, sclerosis, and joint-space widening, narrowing, or partial ankylosis.

●Grade 4: Total ankylosis of joints **(9).**For early diagnosis of axSpA, depending solely on CR is inadequate and may delay treatment **(8).**

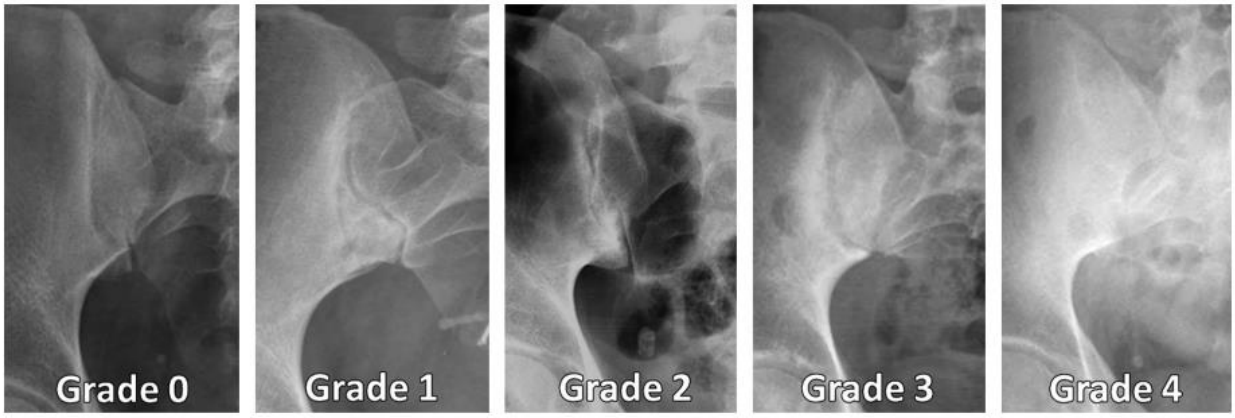


Figure (1): *Radiographic grading of sacroiliitis according to the modified New York criteria* **(10).**

Computed Tomography

CT has superior sensitivity and specificity compared to CR in the visualization of subtle bone erosions, sclerosis, and ankylosis at the SIJ, posterior elements of the spine, and costovertebral joints. CT of the spine is not included in any recommendations as a recommended method of the spine structural damage assessment **(7).**

Even though CT results in an increased amount of radiation compared to CR, it can be helpful in patients with negative CR and unable to undergo MRI or when there are equivocal MRI abnormalities **.** However, it does not detect inflammatory lesions in early axSpA before structural damage occurs. If a CT is considered, a low-radiation CT of the SI joint should be ordered, which is normally satisfactory **(11).**

Ultrasonography

US is an imaging technique increasingly used by rheumatologists in daily clinical practice. Even though contrast-enhanced Doppler US has been noted to have a high negative predictive value for the detection of sacroiliitis, the role of US in examining sacroiliac and spine involvement in AS and other types of axial SpA is minimal **(6).** According to EULAR recommendations US is not recommended for diagnosis of sacroiliitis as a part of axSpA. On the other side, AS and other types of axSpA frequently involve peripheral joints and entheses. US allows assessment of peripheral involvement in SpA **(6).**

Magnetic Resonance Imaging

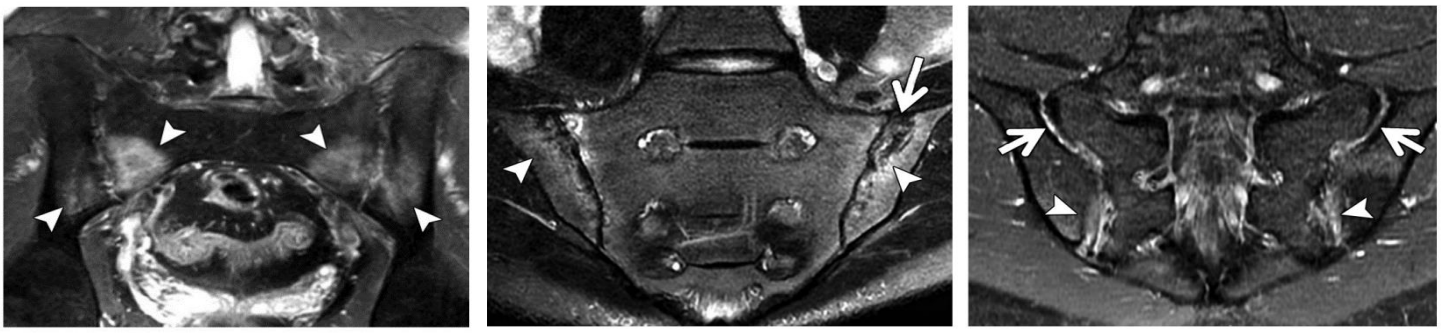
MRI is beneficial for the early diagnosis of axSpA, capable of detecting both BME or osteitis and erosions before CR **(8).**

A pelvic MRI should be regarded if the SIJ radiograph is featureless or doubtful for sacroiliitis and there is persistent clinical doubt for axSpA. An apparent advantage of the MRI is the lack of radiation exposure during the assessment, making it especially helpful in children, young female patients, those with recurrent past radiation exposure, and for recurrent imaging during follow-up **(8).** For sacroiliitis, intravenous gadolinium contrast-enhanced imaging is not recommended by EULAR as it has not been shown to increase diagnostic accuracy and is costly. However, in doubtful cases, it can be used for differential diagnosis **(12).**

MRI, unlike radiography, can demonstrate inflammatory changes, fatty changes, and slight structural abnormalities. Such findings are significant in nr-axSpA because the radiographs in nr-axSpA, by definition, are normal or equivocal. Yet, not all patients with nr-axSpA have anomalous MRI findings, and false-positive findings may emerge in healthy people without axSpA. On the other hand, the MRI of the spine is not typically advised in the diagnostics of axSpA. However, it may be used to assess and observe the axSpA activity. In patients with already diagnosed axSpA, the role of MRI in clinical practice is limited to the differential diagnosis of worsening of spinal symptoms in patients with previously stable clinical disease **(8).**

Subchondral BME involving the sacroiliac joints and entheses are important indicators of early and active inflammatory SpA. Typical locations of BME in patients with axSpA include subchondral or periarticular bone marrow. The lesions are of a high intensity on T2 and give a dark signal in the T1-weighted images **(9).**

Nevertheless, it is not a specific feature for axSpA occurring in other inflammatory and non-inflammatory conditions. In the SIJs, other active inflammatory lesions associated with axSpA, as shown by MRI, though rare as isolated features, include synovitis, enthesitis, and capsulitis **(8).** It is rare for an MRI of definite sacroiliitis to show only one lesion **(9).**



(a) (b) (c)

Figure (2): *Active sacroiliitis in patients with axSpA: (a) Multiple lesions of BME (arrowheads) and erosions. (b) Multiple lesions of BME (arrowheads) and erosions (arrow). (c) Enhancement of the interosseous ligaments (arrows), a finding consistent with enthesitis, as well as periarticular erosions and enhancement (arrowheads) more inferiorly* **(10).**

Nuclear Medicine

Bone scintigraphy was widely used for axSpA-related sacroiliitis detection in the past **(7).** Nevertheless, this technique was superseded by MRI, as a consequence of its low sensitivity, specificity, and accuracy **(13).**

Laboratory Findings

Laboratory findings in AS are generally nonspecific but may aid assist with diagnosis.

CRP and ESR are acute-phase proteins; they are the most widely used inflammatory indicators in active disease status and have been extensively studied in respect of AS. Nevertheless, as diagnostic biomarkers, they have low sensitivity and specificity, increasing only in 40-50% of patients with AS . However, such changes are less frequent in patients with nr-axSpA at approximately 30%. Thus, a normal ESR and CRP should not exclude the disease **(14).**

The CRP metabolite (CRPM) is correlated with disease activity and is significantly increased in AS compared with nr-axSpA. CRP may predict spinal immobility development in AS patients. Moreover, the CRP to albumin ratio (CAR), a novel inflammatory biomarker, is positively correlated with BASDAI and BASFI, being a reliable marker for assessing disease activity in patients with axSpA. CRP levels can predict axSpA treatment response **(15).**

Serum amyloid A protein (SAA) is another inflammatory biomarker more sensitive than other acute-phase proteins but with lower availability and higher cost **(16).**

The serum bone-specific alkaline phosphatase level (ALP) may be raised in severe axSpA. Mild elevation of serum alkaline phosphatase levels was found in 13% of cases with axSpA and associated with high disease activity, more significant structural damage in the SIJs and spine, and lower BMD **(17).**

IgA serum levels are also commonly elevated above the normal range **(9).**

Fibrinogen-to-albumin ratio (FAR) is a novel inflammatory index that is inexpensive and easily measurable. Fibrinogen is also considered an acute-phase response protein able to reflect the systemic inflammatory status. FAR may be used as an inflammatory parameter for monitoring disease activity in AS **(18).**

Normochromic normocytic anemia is occasionally noticed, most commonly in patients with very active disease

HLA-B27 is an MHC class I antigen and a pivotal factor of the WHO classification criteria for axSpA. Some studies have demonstrated that HLA-B27 can predict treatment response and may also be valuable in predicting clinical manifestations **(18).**

Testing for HLA-B27 may be helpful in diagnostic assessments. Human leukocyte antigen B27 positivity occurs in 70% to 90% of White patients with AS but less than 10% of the general population ; yet, the prevalence of AS in the White population with HLA-B27 positivity is around only 5%. Analyses in patients with nr-axSpA have documented the prevalence of HLA-B27 positivity at 74% to 86%, but these estimations should be interpreted cautiously because HLA-

B27 positivity was used as a criterion for identifying these patients. Therefore, HLA-B27 positivity isolated is not diagnostic for axSpA, and a lack of a positive HLA-B27 test does not exclude the diagnosis **(19).**

Lipid levels are decreased during disease activity with, especially high-density lipoprotein cholesterol, resulting in a more atherogenic lipid profile **(20).**

Synovial fluid findings are typical of inflammatory arthritis, with an elevated WBC count dominated by polymorphonuclear leukocytes **(9).**

Upregulation of eight proteins has recently been identified in the SF of AS patients compared to that of the disease control groups, including haptoglobin, matrix metalloproteinase-1, matrix metalloproteinase-3, and serum amyloid P-component, complement factor H-related protein 5, mannose-binding lectin 2, complement component C9, and complement C4-A. These proteins may act as diagnostic or prognostic biomarkers in patients with AS and may enhance this serious disease's clinical results **(21).**

Management

The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) guidelines 2019 updates advise that the objectives of axSpA/AS management are: to relieve symptoms, enhance functioning, sustain workability, reduce disease complications, and diminish skeletal damage. However, patients and physicians often have different perspectives on the management of axSpA/AS. While physicians focus more on pain and stiffness, patients may equally prioritize the impact of illness on work, friends, and family. Identifying patients' requirements is crucial to optimize treatment in axSpA **(22).**

NSAIDs and proper rehabilitation programs remain the mainstays of the management of axSpA. The 2016 update of the Assessment of Spondylarthritis International Society (ASAS) and European League Against Rheumatism (EULAR) guidelines advise that patients with pain and stiffness should utilize an NSAID as a first-line treatment up to the full dose while considering hazards and benefits. For patients who improve on NSAIDs, continued use of this medication is favored if on-demand use worsens symptoms **(20).**

The 2019 ACR/SAA/SPARTAN guidelines recommend that adults with active axSpA obtain continuous NSAIDs over only when required NSAIDs. However, in adults with stable axSpA, only when required treatment with NSAIDs is advised over continued treatment. BDMARDs improve clinical manifestations in patients with axSpA/AS. Remission or low disease activity are the main therapy goals for the disease and indicators of the efficacy of bDMARDs **(22).**BDMARD treatment often persists indefinitely in clinical practice to fulfill these preferred results and sustain disease management. Despite the proper choice, dosing, and adherence of bDMARDs, many patients with axSpA/AS discuss adjusting their biologics with their physicians **(22).**

One of the challenges with biological therapy is the 'wear-off' between doses, reflecting the knowledge of diminished treatment efficacy. Patients with axSpA/AS may experience wear-off as

deteriorating manifestations before each dose, resulting in patients using supplemental medications to control signs and symptoms or demanding modifications in their medication **(22).**

The discovery of anti-TNF has revolutionized the control of AS. IL-17 was later discovered as an alternative therapeutic target. Anti-TNF agents (adalimumab, certolizumab etanercept, golimumab, infliximab) are authorized to manage r-axSpA in Europe and the US. Moderate to high-level quality evidence reinforces the clinically significant efficacy of these agents compared with a placebo for improvement in disease activity and function and fulfilling partial remission in AS in the short term. For nr-axSpA, four drugs (adalimumab, etanercept, Certolizumab, and golimumab) have been indicated. The US has approved Certolizumab to manage nr-axSpA **(23).**

In the 2019 ACR-SAA-SPARTAN guidelines, tofacitinib, a JAK inhibitor, is highlighted as a potential second-line treatment for patients with contraindications to a TNFi other than infections. ACR-SAA-SPARTAN does not advise discontinuation of biologics to avoid symptom recurrence. If tapering is considered, patients should be advised regarding the possibility of increased disease activity**.** Biosimilars are biologic medicines highly equivalent to an approved biologic reference product developed by an originator company. ACR-SAA-SPARTAN strongly advises adults with stable AS to receive an originator anti-TNF and continue treatment with the originator anti-TNF over the required switching to its biosimilar**(23).**Switching should be established on a shared decision-making strategy between patients and rheumatologists, should be a clinically informed decision not made just for economic reasons, and should take contextual aspects of the healthcare system into account. The availability of biological therapies has considerably enhanced the clinical results for patients with axial axSpA. Accordingly, targeting clinical remission/inactive disease is now a possible primary treatment objective as outlined in international recommendations. The concept of treat-to-target (T2T) was imported from diseases like HTN and DM, where clear targets have been defined and validated. It is a treatment strategy in which the clinician treats the patient aggressively to achieve and keep specified and sequentially measured objectives, such as remission/ inactive disease or low disease activity **(24).**

An essential line in managing patients with axSpA is the non-pharmacological treatment modalities. ASAS-EULAR advises that patients should be educated about axSpA and motivated to exercise regularly and discontinue smoking; physical therapy should be regarded **(20).**Including aerobic elements, cardiorespiratory exercises, and educational programs in standard exercise programs may lead to improved clinical results. However, the most helpful exercise protocol must be clarified. Cardiorespiratory and strength exercises have encouraging outcomes on emotional distress, fatigue, and capacity to do a full day's activities were shown in a study in patients with axSpA **(25).**

The T2T concept in axSpA is indirectly supported by connections between levels of axSpA disease activity (mainly Ankylosing Spondylitis Disease Activity Score (ASDAS)) and prospective radiographic progression but lacks potent direct proof. The 2019 ACR-SAA-SPARTAN recommendations documented that focusing on a specific target could lead to rapid cycling through all currently available treatments in some patients. The 2016 update of the ASAS/EULAR

guidelines for the management of axSpA advises that treatment should be guided according to a predetermined treatment goal. This guideline also recommends that the target be shared between the patient and rheumatologist, considering all relevant situational aspects. **(20).**

The 2017 international task force update of guidelines on T2T in axSpA and PsA recommends that the management goal should be clinical remission/inactive disease of musculoskeletal and extra-articular symptoms. In axSpA, the ASDAS is a favored measure to determine the goal **(23).**

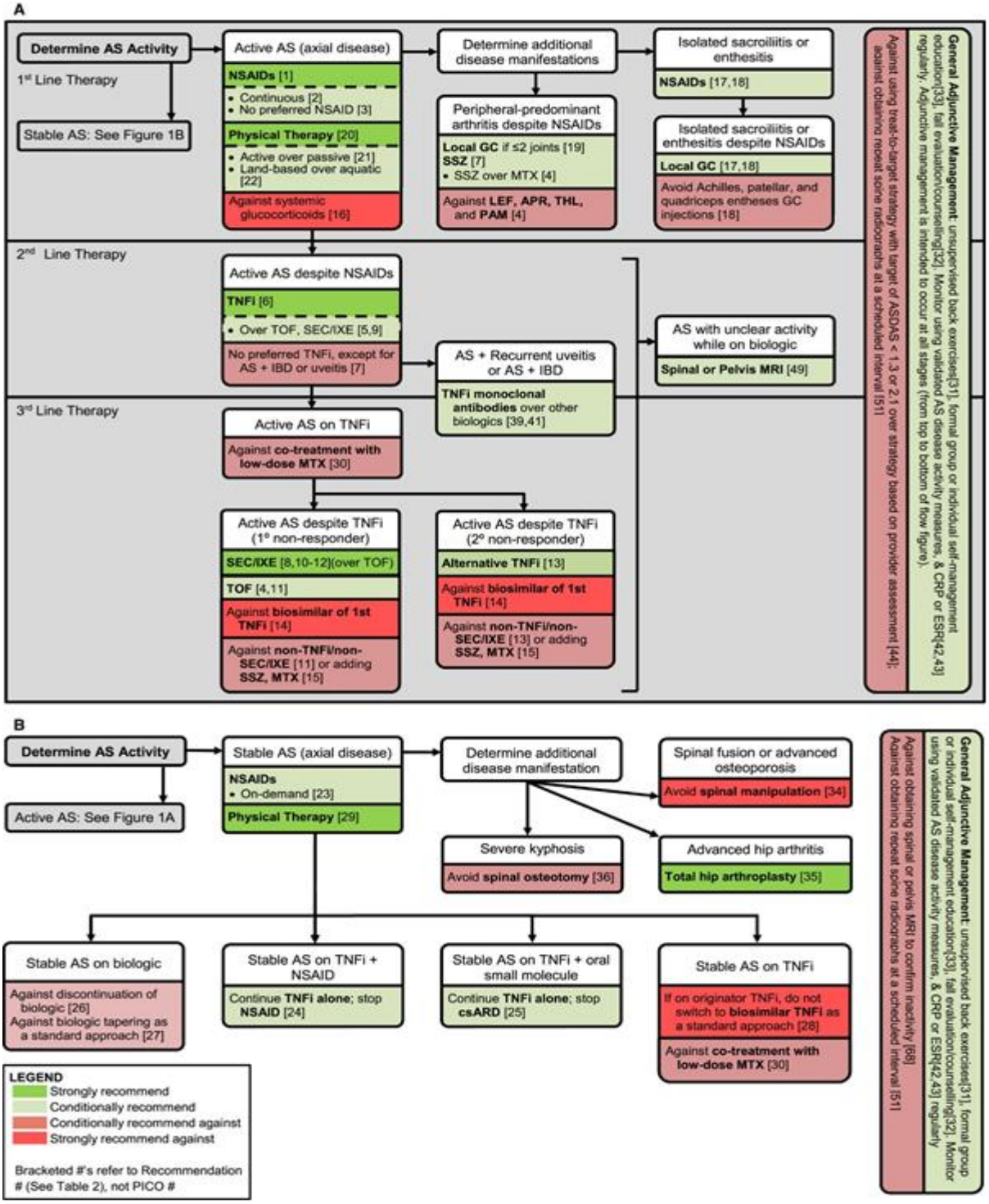


Figure (3): *Summary of the main recommendations for the treatment of patients with A, active AS and B, stable AS.* **(26).**

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